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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/506,942	BALLOUL ET AL.	
	Examiner	Art Unit	
	Shanon A. Foley	1648	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-44 and 46-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-44 and 46-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

The request filed on 10/31/01 for a Request for Continued Examination (RCE) under 37 CFR 1.114 is acceptable. An action on the RCE follows. This action is also responsive to applicant's arguments the amendment filed 9/24/01 of paper no. 10.

Applicant has cancelled claims 23, 24, and 45 in paper no. 10, filed 9/24/01 and has amended claims 32, 39-42, 44, 46, 48, 52, and added new claims 57-80. Claims 32-44 and 46-80 are under consideration.

Claim Objections

Claim 44 is objected to because of the following informalities: "fro" in line 3 is presumably "for".

Claim 53 is objected to because of the following informalities: the claim has a comma at the end of the sentence instead of a period.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-44 and 46-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 32 and 44 are a composition comprising one or more recombinant vectors that encode at least one early polypeptide and at least one late polypeptide from the

papillomavirus, with the exception of a DNA sequence encoding E7 and L2. Subsequent dependent claims 39-42 and state that the early polypeptides E6 and/or E7 and L1 and/or/L2. In addition, independent claim 65 states that the composition includes one late and one early protein from the papillomavirus, which would include the combination E7 and L2. Therefore, it is unclear which ingredients Applicant intends for the vectors to express. This rejection also affects all dependent claims.

Applicant states on page 12 of the amendment that the claims are not contradictory since subsequent claims depend from claim 32 incorporate the negative limitation of the composition lacking L2 and E7 components.

Applicant's arguments have been considered, but are found to be unpersuasive. Dependent claims 39-42 and state that the early polypeptides E6 and/**or** E7 and L1 and/**or** L2. Therefore, the compositions of the dependent claims are contradictory to the independent claim. In addition, the components in new claim 65 do not exclude E7/L2 and broadly encompasses any combination of early and late polypeptides to be expressed by the vectors, which includes the E7/L2 combination.

Claim 32 is also confusing for reciting in lines 1 that the composition comprises one or more vectors, but lines 7-8 state that the composition does not comprise one or more recombinant vectors. The claim is self-contradictory and it cannot be discerned what applicant intends. This rejection affects claims 33-43, 53, 54, 57, and 58.

Claims 57 and 58 recite the limitation "variant" in line 1, respectively. There is insufficient antecedent basis for this limitation in the claim. In addition, the metes and bounds

for what would constitute a "variant" of nononcogenic polypeptides E6 and E7 have not been defined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-44 and 46-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The added material which is not supported by the original disclosure is as follows: claims 32 and 44 are drawn to at least one early polypeptide and one late polypeptide from the papillomavirus to be expressed in one or more vectors, with the specific exception of E7 and L2 combination. This negative limitation cannot be found in the original disclosure.

Applicant submits *In re Wright*, 866 F.2d 422 (Fed. Cir. 1989), which states that exclusionary language that is adequately described in the specification when the specification is read in view of the prior art and argues that the specific exclusion of the E7/L2 combination. Additionally, applicant cites prior art to support the exclusion of the E7/L2 combination.

Applicant's arguments have been carefully considered. However, the courts have found that any negative limitation or exclusionary proviso must have basis in the original disclosure. The mere absence of a positive recitation is not basis for an exclusion. See *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). Therefore, since the

negative limitations excluding undesirable features were not present in the original claims or specification, the new negative limitations constitute new matter.

Claim 32 contains additional material not supported by the original disclosure as follows: lines 7-8 of the claim state that the composition does not comprise one or more recombinant vectors. This negative limitation also cannot be found in the original disclosure. This rejection also affects dependent claims 33-43, 53, 54, 57, and 58.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 32-34, 39-43, 53, and 54 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanley (US 6,096,869).

The claims are drawn to a composition comprising one or more recombinant vaccinia vectors encoding at least one early (E6 or E7 or E6 and E7) and at least one late polypeptide (L1 or L2 or L1 and L2) from a papillomavirus that is used to treat papillomavirus infection.

Stanley et al. teaches a pharmaceutical composition comprising a vaccinia vector encoding at least one papillomavirus protein E1, E2, E4, E5, E6, E7, L1, and/or L2, see column 3, line 63-column 4, line 3 to treat papillomavirus infections, see column 2, line 56-column 3, line 2, and claims 1, 2, 5, 6, 10-13.

Applicant argues that previously cited reference, Stanley et al. (WO 96/29091), does not anticipate the invention because the reference does not teach using recombinant vectors expressing papillomavirus polypeptides in the absence of IL-12.

Applicant's arguments have been considered, but are unpersuasive because the open claim language, "comprising" permits other ingredients, such as IL-12 into the composition. Therefore, since Stanley et al. teaches every element in claims 32-34, 39-43, 53, and 54, Stanley et al. anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 44, 46, 48, 49, 52, 55, 56, 59, 60, 65-67, 72-74, and 78-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al. as applied to claims 32-34, 39-43, 53, and

54 above, and further in view of Hines e al. (Hines et al. Obstetrics and Gynecology. 1995; Vol. 86. No.5, pages 860-866).

The claims are drawn to a composition comprising one or more recombinant vaccinia vectors encoding at least one early (E6 or E7 or E6 and E7) and at least one late polypeptide (L1 or L2 or L1 and L2) from a papillomavirus that is used to treat papillomavirus infection. The composition additionally comprises a vector encoding a polypeptide having immunostimulatory activity, such as IL-2.

See the teachings of Stanley et al. above. Stanley et al. teaches administering immunostimulatory polypeptide, IL-12 in the papillomavirus treatment composition, see previous citations and does not teach administering IL-2 with the treatment composition.

However, Hines et al. teaches that the E7 oncoprotein peptide injected into mice induces a protective cell-mediated response against tumor formation after a challenge with HPV 16-transformed tumor cells *in vivo*. Immunization with peptides prevents tumor formation. Hines et al also teaches cell adoptive therapy treatment to accelerate tumor regression by stimulating their lymphocytes *in vitro* with a peptide, E6 and E7, and a cytokine, IL-2, which is returned to the cancer patient as therapy, see the "cellular adoptive therapy" section on page 862-863 and figure 2 on page 863.

One of ordinary skill in the art at the time the invention was made would have been motivated to express IL-2 in the composition of Stanley et al. to stimulate a cellular immune response against papillomavirus tumor formation *in vivo* to eliminate the time-consuming step of extracting, stimulating, and re-administering peripheral blood lymphocytes (PBMC) back into patients. Also, administering the IL-2 in the vector form would eliminate the possibility of

contaminating the patient's PBMC before re-administration. One of ordinary skill in the art would be further motivated to express IL-2 in the vector composition of Stanley et al. to control the amount of expression of the cytokine and to increase opportunities for the cytokine stimulate more T cells than would be possible to isolate from a single extraction for *ex vivo* stimulation in culture. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because Stanley et al. teaches how one expresses a cytokine in a vaccinia vector in a papillomavirus treatment composition. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Applicant argues that Stanley et al. does not provide sufficient guidance to suggest a reasonable expectation of success for using other stimulatory molecules other than IL-12.

Applicant's arguments have bee considered, but are found to be unpersuasive because the motivation to use the natural stimulating effect of IL-2 of cytotoxic T cells in the vector composition of Stanley et al. is found in the teachings of Hines et al. to stimulate the immune system against a papillomavirus tumor. Further motivation is drawn from natural inclinations of the ordinary artisan to efficiently and specifically stimulate as many T cells *in vivo* against a papillomavirus infection as possible.

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al. and Hines et al. as applied to claims 32-34, 39-44, 46, 48, 49, 52-56, 59, 60, 65-67, 72-74, and 78-80 above, and further in view of Gajewski (The Journal of Immunology. 1996; Vol. 156, pages 465-472).

The claim is drawn to using B7.1 as the immunostimulatory polypeptide.

See the teachings of Stanley et al. and Hines et al. above. Stanley et al. and Hines et al do not teach using B7.1 as the immunostimulatory polypeptide in a papillomavirus composition.

Gajewski teaches that T cells require the participation of one additional "second signal", B7.1, to secrete IL-2. Gajewski also teaches that this aspect of cytotoxic T lymphocytes (CTL) would have a practical application in the development of tumor-specific immunotherapy, see the introduction on page 465. Expression of B7.1 human tumor cells can render them better able to stimulate alloreactive CD8+ lymphocytes to produce their own IL-2, see the first paragraph of the discussion section on page 470.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate B7.1 into the vaccinia composition used to treat papillomavirus infections taught by Stanley et al. to provide a co-factor stimulate T cells to secrete natural IL-2. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because Stanley et al. and Hines et al. use immunostimulatory molecules in compositions to treat papillomavirus tumors and Gajewski teaches that B7.1 is useful for tumor-specific immunotherapy. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Applicants argue that Gajewski has no relevance to the instant invention because the reference is directed to using a cellular composition to treat a cancer patient.

Applicant's arguments have been considered, but are found to be unpersuasive because papillomavirus causes a type of cancer that also requires treatment.

Claims 35-37, 61-63, and 68-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al., Hines et al. as applied to claims 32-34, 39-44, 46, 48, 49, 52-56, 59, 60, 65-67, 72-74, and 78-80 above, and further in view of Boursnell et al. (WO 92/16636).

The claims are drawn to using a Wyeth strain for the recombinant vector and inserting DNA sequences encoding the papillomavirus polypeptides into the TK locus.

See the teachings of Stanley et al. and Hines et al. above. Neither reference teaches using a specific strain of vaccinia as the recombinant vector.

Boursnell et al. teaches a recombinant vector that expresses wild-type or mutant portions of E6 and E7 from HPV16 and HPV18 for conditions caused by an HPV infection, see page 18, lines 1-4. Boursnell et al. teaches that using the Wyeth strain of the vaccinia virus as the vector had the lowest number of complications, see page 14, lines 17-25. The insertion of foreign DNA is favored at the thymadine kinase gene locus; see page 14, lines 26-28 and page 28, lines 22-26. Boursnell et al. also teaches that the p7.5 and/or the H6 promoters may be used, see page 16, lines 11-22.

One of ordinary skill in the art at the time the invention was made would have been motivated to use the Wyeth strain as the vector to encode the papillomavirus polypeptides to lower side effects that could be caused by administration of the vaccine, see Boursnell et al. on page 14, line 17 to page 15, line 12. One of ordinary skill in the art would have had a reasonable expectation for producing the claimed invention because Stanley et al. uses vaccinia to express the papillomavirus polypeptides and Wyeth is a strain of vaccinia. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Applicant argues that Boursnell et al. does not teach a vector-based composition expressing HPV 6, E7, and E6/E7, or an immunostimulatory polypeptide to treat papillomavirus diseases.

Applicant's arguments have been considered, but are found to be unpersuasive. Applicant is referred to the claims of Boursnell et al. that describe a vaccinia virus vector encoding HPV E6 or E7 or E6/E7 to treat papillomavirus disease, see page 6, lines 1-10 and page 7, lines 10-12. As applicants have noted, Boursnell et al. does not teach immunostimulatory molecules in the HPV vaccine composition. However, the combined teachings of Boursnell et al. with other references, i.e., Stanley et al. and Hines et al. that do teach using immunostimulatory molecules in conjunction with papillomavirus polypeptides to treat HPV infection, render the invention obvious.

Claims 38, 64, and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al., Hines et al. as applied to claims 35-37, 61-63, and 68-70 above, and further in view of Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038).

The claims are drawn to the recombinant vector being the MVA strain wherein the DNA sequences of the polypeptides are inserted into at least one incision regions of the viral vector.

See the teachings of Stanley et al. and Hines et al. above. Neither reference teaches using the MVA strain.

Meyer et al. teaches six major deletion sites in the wild-type vaccinia Ankara strain during attenuation to MVA that are not essential to viral replication and attenuate virus pathogenicity, see the abstract, the results section on page 1032-1034. In addition, Meyer et al. teaches that the insertion of the K1L gene of the MVA vaccinia strain leads to increased host

range and suggests this as a selection system for recombinant viruses expressing foreign genes, see page 1037, a third of the way down page 1037. Therefore, one of skill in the art at the time the invention was made would have been motivated to utilize the a vaccinia strain to express papillomavirus peptides, taught by Stanley et al., in a vaccine to treat the papillomavirus because of the large insertion areas provided by the non-essential viral genome that can be deleted without harming viral replication taught by Meyer et al. and to lower side effects that could be caused by administration of the vaccine, see Boursnell et al. on page 14, line 17 to page 15, line 12. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Stanley et al. teaches how to express papillomavirus and immunostimulatory proteins in a vaccinia vector to treat papillomavirus infections and Meyer et al. uses a type of vaccinia virus that allows expression of large inserts. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Applicant argues that Meyer et al. does not suggest expressing HPV polypeptides in the MVA vector.

Applicant's arguments have been considered, but are found to be unpersuasive because Stanley et al. uses a vaccinia virus vector to express multiple HPV polypeptides. Therefore, it would be obvious for one of ordinary skill in the art to choose a vaccinia strain that is capable of expressing multiple genes.

Claims 50, 51, 57, 58, 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al. and Hines et al. as applied to claims 32-34, 39-44, 46, 48, 49, 52-56, 59, 60,

65-67, 72-74, 78-80 above, and further in view of Crook et al. Crook et al. Cell. 1991 ; Vol. 67, pages 547-556 and Munger et al. The EMBO Journal. 1989; Vol. 8, pages 4099-4105.

See the teachings of Stanley et al. and Hines et al. above. Neither reference teaches a nononcogenic E6 or E7 polypeptides consisting of specific deletions.

However, Crook et al. teaches loss of the wild-type tumor suppressor function is achieved by the expression of HPV-16, see the last paragraph of column 1 on page 547. Crook et al. also teaches that an amino acid mutation in E6 reduces binding to p53 by 94% by deleting amino acids 111-115. Munger et al. teaches that E7 disrupts the retinoblastoma (RB) tumor suppressor gene by forming a complex with RB, see the abstract on page 4099. Munger et al. also teaches that the amino acid sequences necessary to form the complex formation with RB is located at a small stretch of amino acids surrounding the cysteine residue at sequence position 24, see the last 2 sentences of the introduction on page 4099. One of ordinary skill in the art at the time of the invention would have been motivated to utilize the specific deletions taught by the references to significantly decrease or eliminate tumor suppression in these proteins. The combined references of Stanley et al., Munger et al., and Crook et al. render the invention as a whole prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley/SAF
December 29, 2001

James C. Housel
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